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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/345,373	07/01/1999	STEVEN M. RUBEN	1448.036000A	1167

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05/13/2002

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EXAMINER

SAOUD, CHRISTINE J

ART UNIT	PAPER NUMBER
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1647

DATE MAILED: 05/13/2002

15

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary

Application No.

09/345,373

Applicant(s)

RUBEN et al.

Examiner

Christine Saoud

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-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136 (a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☒ Responsive to communication(s) filed on Mar 14, 2002.
- 2a) ☒ This action is **FINAL**. 2b) ☐ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11; 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 43-45, 94-126, and 135-200 is/are pending in the application.
- 4a) Of the above, claim(s) 43-45, 94-126, and 135-182 is/are withdrawn from consideration.
- 5) ☐ Claim(s) _____ is/are allowed.
- 6) ☒ Claim(s) 183-200 is/are rejected.
- 7) ☐ Claim(s) _____ is/are objected to.
- 8) ☐ Claims _____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on _____ is/are a) ☐ accepted or b) ☐ objected to by the Examiner.
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
- 11) ☐ The proposed drawing correction filed on _____ is: a) ☐ approved b) ☐ disapproved by the Examiner.
If approved, corrected drawings are required in reply to this Office action.
- 12) ☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

- 13) ☐ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
a) ☐ All b) ☐ Some* c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
2. ☐ Certified copies of the priority documents have been received in Application No. _____
3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).
*See the attached detailed Office action for a list of the certified copies not received.
- 14) ☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).
a) ☐ The translation of the foreign language provisional application has been received.
- 15) ☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

- 1) ☐ Notice of References Cited (PTO-892) 4) ☐ Interview Summary (PTO-413) Paper No(s). _____
- 2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948) 5) ☐ Notice of Informal Patent Application (PTO-152)
- 3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s). _____ 6) ☐ Other:

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DETAILED ACTION

Response to Amendment

1. Claims 127-134 have been canceled and claims 183-200 have been added as requested in the amendment of paper #14, filed 14 March 2002. Claims 43-45, 94-126, 135-182 and 183-200 are pending in the instant application. Claims 43-45, 94-126, and 135-182 stand withdrawn from prosecution as being drawn to a non-elected invention.
2. The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.
3. Any objection or rejection of record which is not expressly repeated in this action has been overcome by Applicant's response and withdrawn.
4. Applicant's arguments filed 14 March 2002 have been fully considered but they are not deemed to be persuasive.

Claim Rejections - 35 USC § 112

5. Claims 183-200 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for an isolated polypeptide comprising an amino acid sequence identical to Ser (69) - Ser (208) of SEQ ID NO:2, does not reasonably provide enablement for

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polypeptides having 90-97% amino acid sequence identity to said sequence for the reasons of record in paper #12 as applied to previously examined claims 127-134. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

Applicant asserts at page 6 of the response that "mere unpredictability of the result of the experiment is not a consideration" for determining whether experimentation is undue. This is not persuasive as the instant rejection was based on careful consideration of all the factors outlined in *In re Wands*. Applicant argues that methods of making and screening polypeptides having the recited % identity are known and that determining which of those possesses a disclosed utility does not require undue experimentation. This argument is not persuasive because Applicant is arguing that as long as one can test for an activity, it is not undue experimentation to make any polypeptide and screen for an activity. This argument completely ignores many of the factors of *In re Wands*, including the lack of examples in the specification, the lack of guidance in the specification and the prior art (as no polypeptides which differ from SEQ ID NO:2 have been generated), the number of embodiments encompassed by the claims, and the unpredictability of the art to which the instant claims are directed. In order to use the claimed invention, the polypeptides which are claimed would need to retain the activity (immunogenic or biological) of the polypeptide which has the amino acid sequence of SEQ ID NO:2 in order for one of ordinary skill to use what is claimed. The instant specification provides no guidance as how to modify the disclosed polypeptide and obtain a protein which has the activity of the native polypeptide (SEQ

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ID NO:2). The specification provides no guidance as to which amino acids (i.e. structural elements) of the native proteins are critical to the biological/immunological activity or which amino acids could be altered without destroying these activities. Without this type of guidance, the skilled artisan does not have a reasonable expectation of making a polypeptide which has any amino acid variation from the disclosed polypeptide and obtaining a functional protein that retains the activity of the native protein, which is necessary for one to use the claimed invention.

Applicant asserts at page 8 of the response that the specification only needs to enable an artisan to make the claimed polypeptides and practice a single use of the claimed polypeptides without undue experimentation. This point is noted and is not in conflict with the instant rejection. Applicant argues that the specification teaches antigenic regions of polypeptide of SEQ ID NO:2 and that "one of ordinary skill in the art, using the guidance provided in the specification, would know not to alter at least one of the antigenic regions disclosed in the specification in order to obtain a polypeptide useful for raising antibodies". This argument is not persuasive because antibodies are generally raised to polypeptides which are injected into animals. The instant specification fails to teach how the antigenic regions would be affected by amino acid substitutions/deletions/insertions in that such modifications would alter the folding of the protein, and therefore, create and/or destroy antigenic sites. These modifications would necessarily generate new proteins which would more likely than not have new and/or different antigenic sites, thereby resulting in antibodies which may or may not recognize the native protein. Therefore, because there is no guidance on how the polypeptide of SEQ ID NO:2 could or should be altered,

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because no examples are provided which demonstrate how the polypeptide of SEQ ID NO:2 could or should be altered, because the art of amino acid substitution is unpredictable, because the number of embodiments encompassed by the claims is vast, because there is no guidance in the prior art as to how to modify the polypeptide of SEQ ID NO:2, the experimentation required to practice the instant claims would be undue.

Applicant asserts at page 10 of the response that pages 152-160 of the specification provide numerous examples of amino acid substitutions. However, a review of this section of the specification reveals that although point mutations are indicated, the mutants have never been tested to determine if biological activity is retained. These “examples” are not sufficient to provide guidance for making modifications to the polypeptide of SEQ ID NO:2 because it is still not known if biological activity is maintained or not. Applicant argues at page 10 of the response that the skill in the art is high and that “practitioners making the polypeptides of the invention are prepared to screen for antibody activity”. This argument is not persuasive because, while some screening is not undue, the necessity to screen each and every mutant encompassed by the claims without a reasonable expectation that any one embodiment will function in a manner to make it useful is undue. This appears to be equivalent to claiming a protein by an activity without teaching what structure is necessary to provide the activity. The claims recite some degree of sequence identity to SEQ ID NO:2, but as no guidance in the specification is provided for which amino acids should be altered and which amino acids should be left unchanged, such modifications are purely random and the claimed proteins are merely a “wish to know”.

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Applicant argues that "proteins are functionally resilient to modification" (see page 11 of the response) and cites Bowie et al. for support of this argument. However, these statements were based on single amino acid substitutions, whereas the instant claims are directed to multiple amino acid substitutions/deletions/insertions. Additionally, Bowie states that while some amino acids play no role in the function of a protein, some amino acids cannot be altered at all. Again, one must realize that these experiments were based on amino acid substitution, and fail to provide guidance for deletion or insertions. The skilled artisan understands that a protein has a primary, secondary and tertiary structure and that many proteins that function as ligands for receptors have amino acids which bind to the receptor site. These amino acids are critical to receptor activation. However, the surrounding amino acids are also important for the proper folding (secondary and tertiary structure) of the protein. Bowie et al. reveals nothing about how deletions and insertions will affect protein function and reveals nothing about multiple mutations as encompassed by the instant claims. Without guidance as to critical amino acids for the function of the protein of SEQ ID NO:2, the skilled artisan would be required to randomly alter the sequence of the protein and screen each embodiment in order to determine which mutants would be useful. Without guidance as to which modifications could or should be made and in view of the lack of predictability and the vast number of embodiments encompassed, it would require undue experimentation to practice the invention as claimed.

Applicant refers to Wands and states that hundreds of clones had to be screened to find one that met the limitations of the claims. However, Wands provided a method of making an

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will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

8. This application contains claims 43-45, 94-126, and 135-182 drawn to an invention nonelected with traverse in Paper No. 11. A complete reply to the final rejection must include cancellation of nonelected claims or other appropriate action (37 CFR 1.144) See MPEP § 821.01.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Christine Saoud, Ph.D., whose telephone number is (703) 305-7519. The examiner can normally be reached on Monday to Friday from 8AM to 3PM. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary Kunz, can be reached on (703) 308-4623.

Certain papers related to this application may be submitted to Technology Center 1600 by facsimile transmission. Papers should be faxed to Technology Center 1600 via the PTO Fax Center located in Crystal Mall 1 (CM1). The faxing of such papers must conform with the notices published in the Official Gazette, 1156 OG 61 (November 16, 1993) and 1157 OG 94 (December 28, 1993) (see 37 C.F.R. § 1.6(d)). NOTE: If Applicant *does* submit a paper by fax, the original signed copy should be retained by Applicant or Applicant's representative. NO DUPLICATE COPIES SHOULD BE SUBMITTED so as to avoid the processing of duplicate papers.

Official papers filed by fax should be directed to (703) 308-4556. If this number is out of service, please call the Group receptionist for an alternate number. Faxed draft or informal communications with the examiner should be directed to (703) 308-0294. Official papers should NOT be faxed to 308-0294.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the Group receptionist whose telephone number is (703) 308-0196.

**CHRISTINE J. SAOUD
PRIMARY EXAMINER**

Christine J. Saoud



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